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Vorwort

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Darüber hinaus bietet die Reihe ein Forum für die Berichterstattung über die zahlreichen Kooperationsprojekte des Instituts mit Partnern aus Industrie und Wirtschaft.

Berichterstattung heißt hier Dokumentation des Transfers aktueller Ergebnisse aus mathematischer Forschungs- und Entwicklungsarbeit in industrielle Anwendungen und Softwareprodukte – und umgekehrt, denn Probleme der Praxis generieren neue interessante mathematische Fragestellungen.

Prof. Dr. Dieter Prätzel-Wolters
Institutsleiter

Kaiserslautern, im Juni 2001

An alternative view on global radiotherapy optimization problems

Filka Yaneva, Tabea Grebe, Alexander Scherrer

July 6, 2009

Abstract

The modeling in inverse radiotherapy planning often involves criterion functions that yield global optimization problems. These problems are typically computed with generic global solvers, which do not take the mathematical structure of the criterion functions into account. This work introduces a general class of functions and analyzes their properties. First, a numerical example illustrates how one may exploit these properties for optimizing a single criterion functions. Then the implications of the function class on general radiotherapy optimization problems are studied. Together, these results may serve as a starting point for the design of suitable global solver concepts for this field of application.

AMS classification: 90C26, 92C50, 52A30, 65K05

Keywords: radiotherapy planning, path-connected sublevelsets, modified gradient projection method, improving and feasible directions

1 Introduction

Radiotherapy is one of the major forms in cancer treatment. The patient is irradiated with high-energetic photons or charged particles with the primary goal of delivering sufficiently high doses to the tumor tissue while simultaneously sparing the surrounding healthy tissue. The inverse search for the treatment plan giving the desired dose distribution is done by means of numerical optimization [11, Chapters 3-5]. For this purpose, the aspects of dose quality in the tissue are modeled as criterion functions, whose mathematical properties also affect the type of the corresponding optimization problem. Clinical practice makes frequent use of criteria that incorporate volumetric and spatial information about the shape of the dose distribution. The resulting optimization problems are of global type by empirical knowledge and typically computed with generic global solver concepts, see for example [16]. The development of good global solvers to

compute radiotherapy optimization problems is an important topic of research in this application, however, the structural properties of the underlying criterion functions are typically not taken into account in this context.
This work introduces a general function class that contains the above mentioned criteria. It then analyses the mathematical properties of these functions, which may facilitate the improvement of already existing solvers and the development of better suited new solvers. A numerical example representing a typical planning situation of clinical routine demonstrates how these mathematical properties could be exploited in the optiimzation of single criterion functions. radiotherapy plan optimization. It concludes with an extension to general radiotherapy optimization problems, which comprises the interplay of several citerion functions in problem formulation and their specific behaviour in plan computation.

2 Terminology

Let each treatment plan be characterized by a vector $\mathbf{x} \geq \mathbf{0}$ of intensity values, and denote by $\mathbb{X}$ the space of treatment plans. Let each dose distribution over a partition of the considered body volume V into small volume elements (voxels) v be described by a vector $\mathbf{d} = (d(v))_{v\in V} \geq \mathbf{0}$ of corresponding dose values, and denote by $\mathbb{D}$ the space of dose distributions. The dose distribution for a treatment plan is obtained with the linear mapping

$$\begin{aligned} \mathbf{d} : \mathbb{X} &\longrightarrow \mathbb{D}, \\ \mathbf{x} &\longmapsto \mathbf{P}\cdot\mathbf{x} = \big(\mathbf{p}(v)\big)_{v\in V}\cdot\mathbf{x} \end{aligned} \tag{1}$$

with the voxel-related row vectors $\mathbf{p}(v) \geq \mathbf{0}$. A planning structure such as a tumor or a healthy organ is characterized by a family of voxels $v \in V' \subseteq V$.
Aspects of dose quality are modeled by criterion functions $f : \mathbb{D} \to \mathbb{R}$. There are various functions in use to measure the overall dose quality on a planning structure V', see [12], which all fulfill some generalized convexity property and thus support the use of convex solver concepts. A well-established criterion is the equivalent uniform dose (EUD) [8],

$$f_{\mathrm{EUD}}(\mathbf{d}) = \Big(\sum_{v\in V'} \mathrm{vol}(v)\cdot d(v)^a \Big)^{\frac{1}{a}} \tag{2}$$

with the structure-specific parameter $a \in (-\infty, 0)\cup[1,\infty)$, where $\mathrm{vol}(v)$ denotes the volume percentage of the voxel with respect to the planning structure V'.
Other common criteria are the so-called physical criteria

$$f_{\mathrm{over}}(\mathbf{d}) = \Big(\sum_{v\in V'} \mathrm{vol}(v)\cdot (d(v) - d_{\mathrm{over}})_+^2 \Big)^{\frac{1}{2}}, \tag{3}$$

$$f_{\mathrm{under}}(\mathbf{d}) = \Big(\sum_{v\in V'} \mathrm{vol}(v)\cdot (d_{\mathrm{under}} - d(v))_+^2 \Big)^{\frac{1}{2}}, \tag{4}$$

which measure the exceedance or undershooting of some reference doses d_{over} and d_{under} respectively [3].
An important feature to assess the volumetric shape of a dose distribution in a planning structure is the cumulative dose-volume histogram (DVH), which provides for each dose value the volume percentage receiving at least this value [15]. The criterion function for the dose d' reads

$$f_{\text{DVH}}(\mathbf{d}) = \sum_{v \in V'} \text{vol}(v) \cdot 1_{[d',\infty)}(d(v)) \tag{5}$$

with the characteristic function $1_{[d',\infty)}$. This function typically enters the optimization problem with upper value bounds to control the occurrence of high dose values in healthy organs or with lower value bounds to limit the undershooting of some prescribed dose in the tumor volume to an acceptably small volume percentage. To show the non-convexity of this criterion, consider a planning structure with two voxels, a first dose distribution with the dose $2d'$ in one voxel and 0 in the other, and a second dose distribution with flipped dose values. Both distributions are mapped to the function value 0.5, but their average receives the value 1.
Another important quality aspect is the occurrence of high dose deposits far outside the tumor. The level sets in the considered volume for certain high dose values d' (isodoses) should pass reasonably close to the tumor and not spread out too far into the healthy tissue. Assigning to each healthy voxel its distance $\text{dist}(v)$ from the tumor, the criterion function can be formulated as

$$f_{\text{Iso}}(\mathbf{d}) = \max_{v \in V'} \Big(\text{dist}(v) \cdot 1_{[d',\infty)}(d(v)) \Big) = \lim_{p \to \infty} \Big(\sum_{v \in V'} \text{dist}(v)^p \cdot 1_{[d',\infty)}(d(v)) \Big)^{\frac{1}{p}} \tag{6}$$

The formulation of planning criteria to control the volumetric and spatial shape of the dose distribution in the tissue is an important topic of current research, see for example [1].

3 General criterion functions

The considered class of criterion functions is defined as

Definition 1 *Let V_m $(m = 1, \ldots, M)$ be planning structures with the voxel-specific weights $\omega_m(v) \geq 0$, the functions $\varphi_m : [0, \infty) \to \mathbb{R}$ $(m = 1, \ldots, M)$ be monotone, and the function $\Phi : \mathbb{R}^M \to \mathbb{R}$ be isotone on $\{(\sum_{v \in V_m} \omega_m(v) \cdot \varphi_m(d(v)))_{m=1,\ldots,M} : \mathbf{d} \in \mathbb{D}\}$. The general criterion function is then defined as*

$$\begin{aligned} f : \mathbb{D} &\longrightarrow \mathbb{R}, \\ \mathbf{d} &\longmapsto \Phi\Big(\big(\sum_{v \in V_m} \omega_m(v) \cdot \varphi_m(d(v)) \big)_{m=1,\ldots,M} \Big) \end{aligned} \tag{7}$$

For the definition of isotone functions, see [10, Definition 2.4.3]. Most of the functions listed in [12] also belong to this class, justifying the notion of a general criterion function. For class definition covering all of those functions, see [13, 14]. For many general criterion functions such as (5) and (6), the following theorem holds.

Theorem 1 *Let $s \geq 0$, f be a general criterion function with increasing component functions φ_m. Then the sublevelset*

$$\mathcal{X}_{\leq s} := \{\mathbf{x} \in \mathbb{X} : \ (f \circ \mathbf{d})(\mathbf{x}) \leq s\} \tag{8}$$

fulfills

$$\mathbf{x} \in \mathcal{X}_{\leq s} \implies \{\mathbf{x}' \in \mathbb{X} : \ \mathbf{x}' \leq \mathbf{x}\} \subseteq \mathcal{X}_{\leq s}$$

and the superlevelset

$$\mathcal{X}_{\geq s} := \{\mathbf{x} \in \mathbb{X} : \ (f \circ \mathbf{d})(\mathbf{x}) \geq s\}$$

fulfills

$$\mathbf{x} \in \mathcal{X}_{\geq s} \implies \{\mathbf{x}' \in \mathbb{X} : \ \mathbf{x}' \geq \mathbf{x}\} \subseteq \mathcal{X}_{\geq s}$$

Proof:
Let $\mathbf{x} \in \mathbb{X}$ with $(f \circ \mathbf{d})(\mathbf{x}) \leq s$, and $\lambda \leq \mathbf{1} \in \mathbb{X}$. The values $\varphi(d(v)(\mathrm{diag}(\lambda) \cdot \mathbf{x})) = \varphi(\sum_{i=1}^{\dim(\mathbb{X})} \lambda_i \cdot (p_i(v) \cdot x_i))$ increase monotonously in λ_i according to the requirements, hence also f attains its maximal value for $\lambda = \mathbf{1}$ and the whole cuboid $\{\mathbf{x}' \in \mathbb{X} : \ \mathbf{x}' \leq \mathbf{x}\}$ belongs to the sublevel set. The proof for the superlevelset is analogous.

Analogous statements hold for decreasing φ_m. This theorem implies the following

Corollary 1 *Under the requirements of Theorem 1, $\mathcal{X}_{\leq s}$ is star-shaped and path-connected, and $\mathcal{X}_{\geq s}$ is path-connected.*

Proof:
The diagonal of the cuboid from $\mathbf{0}$ to $\mathbf{x}$ belongs to the sublevelset, which is thus star-shaped with respect to $\mathbf{0}$ and also path-connected. The complement of the superlevelset, $\mathbb{R}^{\dim(\mathbb{X})} \setminus \mathcal{X}_{\geq s} = (\mathbb{R}^{\dim(\mathbb{X})} \setminus \mathbb{X}) \cup \mathcal{X}_{<s}$ is obviously star-shaped with respect to $\mathbf{0}$ and therefore does not surround any nontrivial subset of $\mathcal{X}_{\geq s}$, which is thus path-connected.

For decreasing φ_m the superlevelsets are star-shaped and path-connected, and the sublevelsets are path-connected.
The statement of Theorem 1 also extends to cones in the following way:

Corollary 2 *Let the requirements of Theorem 1 be fulfilled,* $\mathbf{x}_1, \ldots, \mathbf{x}_N \in \mathbb{X}$ *and* $\Lambda = \{\lambda \in \mathbb{R}^N : \ \lambda \geq \mathbf{0}\}$*. Then the sublevelset*

$$\mathcal{X}^{\Lambda}_{\leq s} := \Big\{ \mathbf{x} = \sum_{n=1}^{N} \lambda_n \mathbf{x}_n : \ \lambda \in \Lambda, \ (f \circ \mathbf{d})(\mathbf{x}) \leq s \Big\} \tag{9}$$

fulfills

$$\sum_{n=1}^{N} \lambda_n \mathbf{x}_n \in \mathcal{X}^{\Lambda}_{\leq s} \implies \Big\{ \sum_{n=1}^{N} \lambda'_n \mathbf{x}_n : \ \lambda' \leq \lambda \Big\} \subseteq \mathcal{X}^{\Lambda}_{\leq s}$$

is star-shaped with respect to $\mathbf{0}$ *and path-connected, and the superlevelset*

$$\mathcal{X}^{\Lambda}_{\geq s} := \Big\{ \mathbf{x} = \sum_{n=1}^{N} \lambda_n \mathbf{x}_n : \ \lambda \in \Lambda, \ (f \circ \mathbf{d})(\mathbf{x}) \geq s \Big\}$$

is path-connected.

Proof:
Writing $\mathcal{X}^{\Lambda}_{\leq s} = \mathcal{X}_{\leq s} \cap \{\sum_{n=1}^{N} \lambda_n \mathbf{x}_n : \lambda \in \Lambda\}$, the proof is analogous to Theorem 1 and Corollary 1.

This corollary addresses the situation in radiotherapy planning, that several treatment plans, each of which fulfilling some of the aspired goals of quality, are interpolated in order to obtain a plan that compromises all goals in a reasonable way. The examplary planning problem in Section 5 demonstrates a similar scenario.
The path-connectedness of its sublevelsets implies, that a general criterion function f is connected in the sense of [10, Definition 4.2.3]. A descent method applied to such a function would produce a sequence of iterates belonging to sublevelsets (8) or (9) for gradually decreasing values [7, page 184]. The connectedness property implies that such sequences approach a global minimum of a general criterion function according to the convergence theorems of [19]. Section 5 gives an illustrative example for this based on the exemplary planning problem of the following section.
The optimization of a single general criterion function can thus be done with highly goal-oriented numerical solvers. However, the presence of multiple such functions in general leads to global optimization problems. This property mainly originates from the interplay of general criterion functions, which is addressed in Section 6.

4 An exemplary radiotherapy planning problem

Figure 1 shows an artificial two-dimensional example of a prostate carcinoma. The half-moon shaped structure in the middle represents the tumor, which consists of 658 voxels, the circular structure below it is the rectum, which comprises

96 voxels, and the structure above the tumor is the bladder with 264 voxels. The remaining area between these planning structures and the elliptic outer body contour is the unclassified tissue with 5310 voxels. The tumor enters the optimization problem with the average underdose (4) with the dose threshold of 66Gy and the average overdose (3) with the threshold of 72Gy. Dose qual-

Figure 1: A artificial two-dimensional prostate carcinoma

ity in the healthy structures is modeled with the EUD (2) with the parameter $a = 6.3$ for the rectum, 3.8 for the bladder and 1.1 for the unclassified tissue [9]. Radiotherapy planning problems are known to be of multi-objective type, see [18] and [6]. In this particular case, the second major goal besides realizing high doses in most of the tumor is a reasonable trade-off between the dose deposits in the bladder and the rectum and the occurrence of high doses in the tumor. The multi-objective optimization problem thus reads

$$\begin{aligned} \left\{ f_{\mathrm{EUD,rectum}}(\mathbf{d}(\mathbf{x})), f_{\mathrm{EUD,bladder}}(\mathbf{d}(\mathbf{x})), f_{\mathrm{over,tumor}}(\mathbf{d}(\mathbf{x})) \right\} &\rightarrow \min \quad (10) \\ f_{\mathrm{under,tumor}}(\mathbf{d}(\mathbf{x})) &\leq 0.5\mathrm{Gy} \\ f_{\mathrm{EUD,unclassified}}(\mathbf{d}(\mathbf{x})) &\leq 30\mathrm{Gy} \\ \mathbf{x} &\in \mathbb{X} \end{aligned}$$

This problem was computed three times by minimizing one of the objective functions and including the two others as additional constraints with the upper value bounds of 60Gy for the rectum EUD and the bladder EUD and 2.5Gy for the tumor overdose. The isodose visualization of the corresponding dose distributions with the isodose lines for 35, 46, 53 and 60Gy are shown in Figure 2. The strong symmetry in the isodoses with respect to the vertical main axis of the elliptic outer contour results from a symmetric positioning of irradiating beams. The first optimization treated the tumor criterion as the objective and gave a plan, whose dose distribution spreads far out into both bladder and rectum. For the second optimization, the bladder criterion was taken as objective, and the isodoses of the resulting dose distribution indicate a good sparing of the bladder for the price of a comparably worse situation in rectum and unclassified tissue. The third plan was optimized with respect to the rectum criterion, and the obtained isodoses pass nicely around this organ, but reach farther into the bladder.

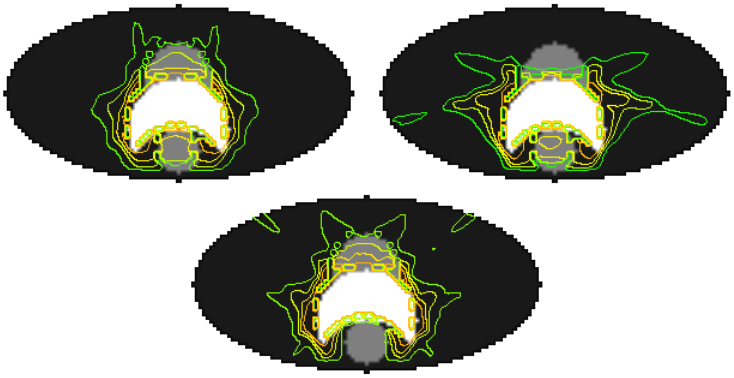

Figure 2: The isodose displays for the computed plans

5 Optimization of a general criterion function

The convex hull of these plans is then used for the search of a plan, which is of reasonable quality in the above planning aspects and minimizes the occurrence of higher dose deposits outside the tumor. The corresponding optimization problem reads

$$\begin{aligned} f_{\mathrm{DVH}}\Big(\mathbf{d}\big(\sum_{n=1}^{N}\lambda_n\mathbf{x}_n\big)\Big) &\to \min \quad \text{s.t.} \\ \mathbf{1}^T\cdot\lambda &= 1 \\ -\mathbf{e}_1^T\cdot\lambda &\le 0 \\ \vdots \quad &\vdots \quad \vdots \\ -\mathbf{e}_N^T\cdot\lambda &\le 0 \end{aligned} \tag{11}$$

where $N = 3$. Figure 3 shows the graph of the criterion function (5) over the convex coefficients for the dose threshold $d' = 35\mathrm{Gy}$. The corner point of the underlying domain in the foreground corresponds to the first plan, the one in the background to the second plan, and the origin to the third plan. The non-convexity of some of the sublevelsets is obvious and the path-connectness for all of them was numerically validated.

For solving this optimization problem with a derivative-based descent method, its objective function was smoothened out by approximating the step function $1_{[d',\infty)}(d)$ with the pseudoconvex function $\varphi(d) = (1 + e^{c\cdot(d'-d)})^{-1}$ with some steepness parameter $c > 0$. The simple structure of the constraints motivate the usage of Rosen's modified gradient projection method. This method converges to KKT points according to [2, Theorem 10.5.7], which are optima of the problem (11) due to the fulfillment of the linear independence constraint qualification. Rosen's method involves iterative steps along $-\mathbf{Q}\nabla f_{\mathrm{DVH}}$ with

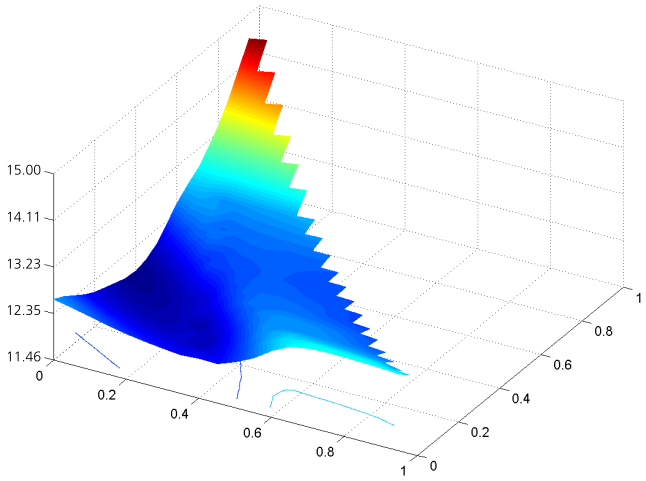

Figure 3: The function graph for $d^{'} = 35\text{Gy}$ displayed over the parameters λ_1 (axis in the foreground) and λ_2 (axis on the right).

the projection matrix $\mathbf{Q} = \mathbf{I} - \mathbf{R}^T(\mathbf{R}\mathbf{R}^T)^{-1}\mathbf{R}$, where the matrix

$$\mathbf{R} = \begin{pmatrix} \mathbf{1}^T \\ -\mathbf{e}^T_{\sigma(1)} \\ \vdots \\ -\mathbf{e}^T_{\sigma(N')} \end{pmatrix} \in \mathbb{R}^{(N'+1)\times N}$$

consists of the active constraint vectors from (11). The simple structure of the constraints gives the projection matrix the following simple structure, which allows for an efficient computation.

Lemma 1 *Let the first $N'+1$ constraints be active and the variables be identically reordered. Then the projection matrix fulfills*

$$\mathbf{Q} = \begin{pmatrix} \mathbf{I}_{(N')} & \mathbf{0} \\ \mathbf{0} & \frac{1}{N-N'} \cdot \mathbf{1}_{(N-N')} \end{pmatrix}$$

where the subscripts denote the dimensions of the quadratic matrices.

Proof:
The full rank of $\mathbf{R}$ implies invertibility for $\mathbf{R}\mathbf{R}^T$ with the inverse

$$(\mathbf{R}\mathbf{R}^T)^{-1} = \frac{1}{N-N'} \cdot \begin{pmatrix} 1 & \mathbf{1} & 1 \\ \mathbf{1}^T & \mathbf{0}_{(N'-1)} & \mathbf{1}^T \\ 1 & \mathbf{1} & 1 \end{pmatrix} + \begin{pmatrix} 1 & \mathbf{1} \\ \mathbf{1}^T & \mathbf{1}_{(N')} \end{pmatrix}$$

and straight-forward computation gives the claim.

Note that the requirements are without loss of generality and can be obtained with appropriate permutations.
The optimization problem (11) was solved for different dose values d' with computation times in the range of just a few seconds [17]. Table 1 lists the criterion values for the three computed plans, the optimal coefficient vectors and the corresponding optimal criterion values. All optima are convex combinations

d'	Plan 1	Plan 2	Plan 3	Optimum	Optimal value
35Gy	12.88	14.95	12.62	(0, 0.38, 0.62)	11.88
46Gy	7.34	8.32	5.83	(0, 0.27, 0.73)	5.73
53Gy	4.35	5.20	3.44	(0, 0.22, 0.78)	3.22
60Gy	1.73	1.77	1.86	(0, 0.39, 0.61)	1.55

Table 1: The criterion values in percent for the three plans, the optimal coefficient vector and the optimal value

of the plans optimized with respect to the bladder and the rectum, for which the isodoses stay closest to the tumor according to Figure 2. Comparison of the optimal values with the criterion values for the original plans and of the corresponding optimal isodoses for 35, 46, 53 and 60Gy as shown in Figure 4 with the isodose shapes of the original plans gives another validation for the non-convexity of the considered general criterion function.

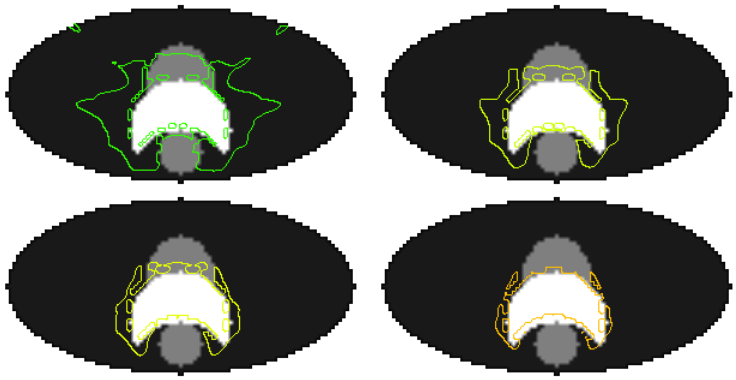

Figure 4: The isodose displays for the optimal plans for 35, 46, 53 and 60Gy

6 General radiotherapy optimization problems

Radiotherapy planning problems mostly incorporate various planning aspects and several planning goals, hence the corresponding optimization problems contain several criterion functions as constraints and also as objectives, see Section

4. In particular, the computation of multi-objective problems requires the combination of the multiple objectives to a single objective function by means of scalarization methods. This implies the question about the interplay of the general criterion functions in problem formulation and plan computation. Since the modeling of planning criteria, their combination to an optimization problem and its computation with a numerical solver are strongly case-specific, the following general considerations are solely intended to address some general aspects.
The combination of planning criteria to an optimization problem can be understood as operations on the function class fulfilling Definition 1. Concerning the constraints, the presence of multiple upper bound constraints $f_{k'}(\mathbf{d}(\mathbf{x})) \leq s_{k'}$ $(k' = 1, \ldots, K')$ can be rewritten as $\max_{k'=1,\ldots,K'}(f_{k'}(\mathbf{d}(\mathbf{x})) - s_{k'}) \leq 0$. Analogously, the case of multiple lower bound constraints means formation of a minimum. The maximum operation also covers the scalarization methods of lexicographic optimization, weighted Tchebycheff and Pascoletti-Serafini, see [4]. Other popular approaches are the weighted scalarization, the elastic constraint method, Benson's method, the smoothed weighted Tchebycheff and the entropically smoothed Pascoletti-Serafini, see [4], which are based on the addition of criterion functions. These operations fulfill the following

Lemma 2 *The class of general criterion functions is closed with respect to the formation of maximum and minimum and with respect to the addition of functions.*

Proof:
Consider two general criterion functions f, f' with the corresponding component functions by $\Phi : \mathbb{R}^M \to \mathbb{R}$, $\Phi' : \mathbb{R}^{M'} \to \mathbb{R}$. Then $\max(\Phi, \Phi') : \mathbb{R}^{M+M'} \mapsto \mathbb{R}$ is monotonously increasing and $\max(f, f')$ thus a general criterion function. The cases of $\min(\Phi, \Phi')$ and $\Phi + \Phi'$ are analogous.

Note that scalings with non-negative factors or shifts by real values also maintain the requirements of Definition 1, which thus supports all the required operations in the interplay of general criterion functions.
These operations are of particular interest for general criterion functions whose component functions φ_m are all either monotonously increasing or monotonously decreasing as addressed in Section 3. Such functions are also of high practical relevance, see for example the radiotherapy optimization problem (10). The constraint of sufficiently high doses almost everywhere in the tumor volume may be also formulated by means of a DVH-based function (5) for some prescribed dose value d' with a lower value bound of 0.95, and the sparing of the healthy organs could be achieved by simultaneously minimizing the values of DVH-based criterion functions for certain critical dose values. General criterion functions with monotonously increasing (decreasing) component functions have star-shaped and path-connected sublevelsets (superlevelsets) ranging from $\mathbf{0}$ into $\mathbb{X}$ and path-connected superlevelsets (sublevelsets) ranging from "infinity" towards $\mathbf{0}$ according to Theorem 1 and Corollaries 1 and 2. The following considerations sketch possible algorithmic exploitations of this "orientation of

sets".
Many optimization algorithms involve movements from the current iterate along improving directions towards lower function values in the sense of [2, Definition 4.2.1]. The improving directions fulfill the following

Lemma 3 *Let f be a general criterion function with increasing component functions φ_m. Then the set of improving directions*

$$\mathcal{X}_{impr}(\mathbf{x}) := \{\mathbf{x}'-\mathbf{x} :\ \mathbf{x}' \in \mathbb{X},\ \exists \xi > 0\ (f\circ\mathbf{d})(\mathbf{x}+\xi'(\mathbf{x}'-\mathbf{x})) < (f\circ\mathbf{d})(\mathbf{x})\ \forall 0 < \xi' < \xi\}$$

fulfills

$$\mathcal{X}_{impr}(\mathbf{x}) \subseteq \mathbb{R}^{dim(\mathbb{X})} \setminus \{\mathbf{x}' - \mathbf{x} :\ \mathbf{x}' \in \mathbb{X},\ \mathbf{x}' \geq \mathbf{x}\}$$

If the monotonicity is strict, then additionally

$$\{\mathbf{x}' - \mathbf{x} :\ \mathbf{x}' \in \mathbb{X},\ \mathbf{x}' < \mathbf{x}\} \subseteq \mathcal{X}_{impr}(\mathbf{x})$$

where $\mathbf{x}' < \mathbf{x}$ means $\mathbf{x}' \leq \mathbf{x}$ with inequality in at least one component.

Proof:
For $\mathbf{x}' \geq \mathbf{x}$, the monotonicity implies $(f \circ \mathbf{d})(\mathbf{x} + \xi'(\mathbf{x}' - \mathbf{x})) \geq (f \circ \mathbf{d})(\mathbf{x})$ for all $\xi' \geq 0$. In case of strict monotonicity, $\mathbf{x}' < \mathbf{x}$ implies $(f \circ \mathbf{d})(\mathbf{x} + \xi'(\mathbf{x}' - \mathbf{x})) < (f \circ \mathbf{d})(\mathbf{x})$ for all $\xi' > 0$.

Analogous statements hold for general criterion functions with monotonously decreasing component functions, and equivalent conclusions can be drawn for the sets of improving directions for the maximization of general criterion functions. These results may be strengthened by incorporating tangential information about the levelset of $f \circ \mathbf{d}$ passing through $\mathbf{x}$, depending on the specific general criterion function in consideration. Note that the strict monotonicity is for example fulfilled by the functions used in Section 5. Hence, the orientation of sublevelsets also implies an orientation for the sets of feasible directions. These properties may be exploited in the algorithmic design of numerical solvers, for example in a more goal-oriented mutation and recombination step of a genetic optimization method, see [5, Chapters 3-4].
The set of improving directions is also used in combination with the set of feasible directions [2, Definition 4.2.1], which retain the validity of active constraints, to formally introduce the notion of optimality, see for example [2, Theorem 4.2.15]. The set of feasible directions fulfills

Lemma 4 *Let f be a general criterion function with strictly increasing component functions φ_m, and let $\mathbf{x} \in \mathbb{X}$ fulfill an upper value bound on $f \circ \mathbf{d}$ with equality. Then the set of feasible directions*

$$\mathcal{X}_{feas}(\mathbf{x}) := \{\mathbf{x}'-\mathbf{x} :\ \mathbf{x}' \in \mathbb{X},\ \exists \xi > 0\ (f\circ\mathbf{d})(\mathbf{x}+\xi'(\mathbf{x}'-\mathbf{x})) \leq (f\circ\mathbf{d})(\mathbf{x})\ \forall 0 < \xi' < \xi\}$$

fulfills

$$\{\mathbf{x}' - \mathbf{x} :\ \mathbf{x}' \in \mathbb{X},\ \mathbf{x}' \leq \mathbf{x}\} \subseteq \mathcal{X}_{feas}(\mathbf{x}) \subseteq \mathbb{R}^{dim(\mathbb{X})} \setminus \{\mathbf{x}' - \mathbf{x} :\ \mathbf{x}' \in \mathbb{X},\ \mathbf{x}' > \mathbf{x}\}$$

Proof:
$\mathbf{x}' \geq \mathbf{x}$ implies $(f \circ \mathbf{d})(\mathbf{x} + \xi'(\mathbf{x}' - \mathbf{x})) \leq (f \circ \mathbf{d})(\mathbf{x})$ for all $\xi' \geq 0$, and $\mathbf{x}' > \mathbf{x}$ implies $(f \circ \mathbf{d})(\mathbf{x} + \xi'(\mathbf{x}' - \mathbf{x})) > (f \circ \mathbf{d})(\mathbf{x})$ for all $\xi' \geq 0$.

General criterion functions with monotonously decreasing component functions imply similar results, and the statements are analogous for the maximization of general criterion functions. A strengthening of these results would require further information about the structure of the corresponding sublevelset. These properties may be analogously exploited in the solver design.
$\mathbf{x}^* \in \mathbb{X}$ is a local optimum, if it fulfills all constraints and any further improvement of the objective function would lead to the violation of a constraint, which means $\mathcal{X}_{\text{impr}}(\mathbf{x}^*) \cap \mathcal{X}_{\text{feas}}(\mathbf{x}^*) = \emptyset$. Depending on the numerical solver in use, Lemmata 3 and 4 may then support the verification of optimality.

7 Conclusions

The development of numerical solvers for radiotherapy planning mainly focusses on the utilization of generic global solver concepts, but widely neglects the structural properties of the involved criterion functions. The unifying function concept introduced in this work and its mathematical properties are intended to provide deeper insight into the structure of the resulting optimization problems. Rosen's method may serve as an example how to exploit the structure of a single general criterion function in numerical optimization by means of appropriate descent methods. The approaches to combine several functions, the conclusions on the improving and feasible directions in the solver iterations and the statements about local optimality sketch the existing possibilities to adapt generic global optimization methods to radiotherapy optimization problems. Altogether, these results may serve as a motivation and starting point for the development of hybrid solver concepts, which combine global methods such as stochastic algorithms with local algorithms such as deterministic descent methods, both suitable to this field of application.

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